

19



Europäisches Patentamt
European Patent Office
Office européen des brevets



11 Publication number:

0 496 237 A2

12

EUROPEAN PATENT APPLICATION

21 Application number: 92100414.9

51 Int. Cl.⁵: C07D 403/10, A61K 31/415

22 Date of filing: 13.01.92

30 Priority: 22.01.91 GB 9101375

43 Date of publication of application:
29.07.92 Bulletin 92/31

84 Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI NL PT SE

71 Applicant: FARMITALIA CARLO ERBA S.r.L.
Via Carlo Imbonati 24
I-20159 Milano(IT)

72 Inventor: Cozzi, Paolo
via Zanella 48/5
I-20133 Milan(IT)
Inventor: Pillan, Antonio
via Milani 1

I-20133 Milan(IT)

Inventor: Pulici, Maurizio

via Giovanni Pascoli 1

I-20056 Grezzago (Milan)(IT)

Inventor: Salvati, Patricia

via Valera 16

I-20020 Arese (Milan)(IT)

Inventor: Volpi, Angelo Daniele

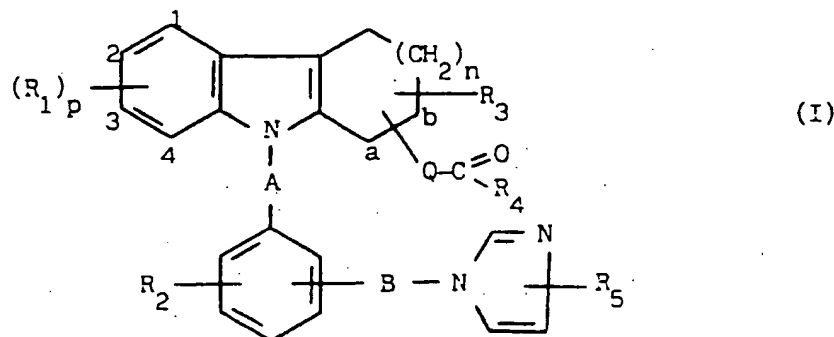
via Cascina Croce 204

I-20010 Cornaredo (Milan)(IT)

74 Representative: Ferrario, Vittorino (IT)
c/o Farmitalia Carlo Erba S.p.A. Via Carlo
Imbonati 24
I-20159 Milano(IT)

54 N-imidazolyl derivatives of substituted tetrahydrocarbazole and cyclohept[b]indole.

57 The invention provides new N-imidazolyl derivatives of substituted tetrahydrocarbazoles and cyclopent[b]-indoles of general formula (I)



wherein

n is 1 or 2;

p is an integer of 1 to 4;

A is a straight or branched C₁-C₄ alkylene chain;

B is a direct linkage, a straight or branched, unsaturated or saturated C₁-C₄ alkylene chain;

Q is a direct linkage or a straight or branched C₁-C₄ alkylene chain;

each of R₁ and R₂ independently is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, halogen or trihalomethyl;

EP 0 496 237 A2

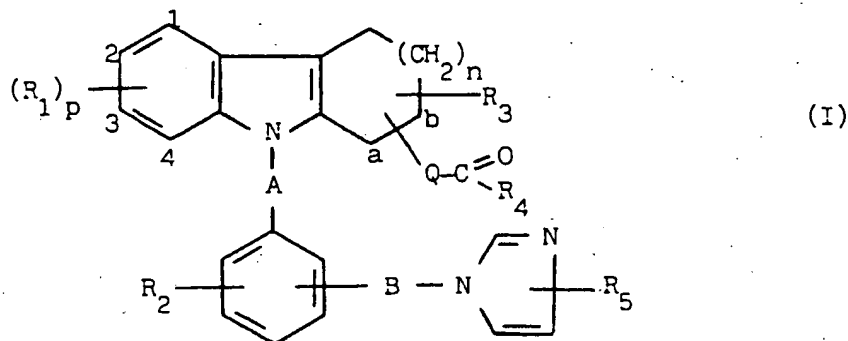
each of R_3 and R_5 , independently is hydrogen or C_1 - C_4 alkyl; R_4 is $-OR_6$ or $-N(R_6, R_7)$ group, wherein each of R_6 and R_7 independently is hydrogen, C_1 - C_4 alkyl, phenyl or benzyl; or a pharmaceutically acceptable salt thereof, which are useful in the treatment of a disease state in which an enhancement of TxA_2 synthesis exerts a pathogenic effect.

The present invention relates to new N-imidazolyl derivatives of substituted tetrahydrocarbazoles and cyclohept[b]indoles, to a process for their preparation, to pharmaceutical compositions containing them and to their use as therapeutic agents. The present invention provides novel compounds having the general formula (I)

5

10

15



20 wherein

n is 1 or 2;

p is an integer of 1 to 4;

A is a straight or branched C₁-C₄ alkylene chain;

B is a direct linkage, a straight or branched, unsaturated or saturated C₁-C₄ alkylene chain;

25 Q is a direct linkage or a straight or branched C₁-C₄ alkylene chain;

each of R₁ and R₂ independently is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, halogen or trihalomethyl;

each of R₃ and R₅, independently is hydrogen or C₁-C₄ alkyl;

30 R₄ is a -OR₆ or -N(R₆,R₇) group, wherein each of R₆ and R₇ independently is hydrogen, C₁-C₄ alkyl, phenyl or benzyl and the pharmaceutically acceptable salts thereof.

The invention also includes within its scope all the possible isomers, stereoisomers and their mixtures and the metabolites and the metabolic precursors or bioprecursors of the compounds of formula (I).

When p is higher than 1, then each R₁ substituent may be the same or different.

35 The substituents R₃ and -Q-C(O)R₄ may be attached to any of the carbon atoms of the cyclohexyl or cycloheptyl moiety.

The alkyl, alkoxy, alkylthio, and alkylsulfonyl groups may be branched or straight chain groups.

A C₁-C₄ alkyl group is e.g. methyl, ethyl, propyl, isopropyl, butyl or tert-butyl, preferably methyl or ethyl.

40 A C₁-C₄ alkoxy group is e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy or tert-butoxy, preferably methoxy, ethoxy or propoxy.

A C₁-C₄ alkylthio group is e.g. methylthio, ethylthio, propylthio or butylthio, preferably methylthio or ethylthio.

A C₁-C₄ alkylsulfonyl group is preferably methylsulfonyl.

A halogen atom is bromine, chlorine or fluorine, preferably bromine or fluorine.

45 A straight or branched C₁-C₄ alkylene chain is -CH₂-, -CH₂-CH₂-, or -CH(CH₃)-CH₂- in particular -CH₂- or -CH₂-CH₂-.

A trihalomethyl group is e.g. trichloromethyl or trifluoromethyl, preferably trifluoromethyl.

A straight or branched, saturated or unsaturated C₁-C₄ alkylene chain is e.g. a chain chosen from -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH(CH₃)-CH₂-, or -CH=CH-, in particular -CH₂- or -CH₂-CH₂-.

50 Pharmaceutically acceptable salts of the compounds of the invention include acid addition salts, with inorganic, e.g. nitric, hydrochloric, hydrobromic, sulphuric, perchloric and phosphoric acids, or organic, e.g. acetic, propionic, glycolic, lactic, oxalic, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic and salicylic acids, and salts with inorganic, e.g. alkali metal, especially sodium or potassium, bases or alkaline-earth metal, especially calcium or magnesium, bases, or with organic bases, e.g. alkylamines, preferably triethylamine, or basic naturally occurring aminoacids, preferably arginine.

55 As stated above the present invention also includes within its scope pharmaceutically acceptable bioprecursors (otherwise known as pro-drugs) of the compounds of formula (I), i.e. compounds which have a different formula to formula (I) above but which nevertheless upon administration to a human being are

converted directly or indirectly in vivo into a compound of formula (I).

Preferred compounds of the invention are the compounds of formula (I), wherein, each of n and p independently is 1 or 2;

- 5 **A** is -CH₂- or -CH₂-CH₂-;
 B is direct linkage or -CH₂-;
 Q is direct linkage, -CH₂- or -CH₂-CH₂-; each of R₁, R₂, independently is hydrogen, C₁-C₄ alkyl, halogen or trifluoromethyl;
 R₃ and R₅ are hydrogen;
 R₄ is -OR₆ or -NHR₆ wherein R₆ is hydrogen or C₁-C₄ alkyl and the pharmaceutically acceptable salts thereof.

10 More preferred compounds of the invention are compounds of formula (I) wherein: each of n and p independently is 1 or 2;

- A** is -CH₂-;
 B is a direct linkage or -CH₂-;
 15 **Q** is -CH₂-;
 R₂, R₃ and R₅ are hydrogen;
 R₁ is halogen or trifluoromethyl;
 R₄ is OR₆ or NHR₆ wherein R₆ is hydrogen or C₁-C₄ alkyl; and the pharmaceutically acceptable salt thereof.

20 Examples of the preferred compound of formula (I) are the following:

- 1) 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ;
- 2) Ethyl 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-2-yl-1,2,3,4-tetrahydrocarbazol-1-yl-acetate;
- 3) 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetamide;
- 4) 6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
- 25 5) Ethyl 6,8-difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate;
- 6) 6-Fluoro-9-[[3-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ;
- 7) 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid ;
- 8) 6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid;
- 9) 6-Fluoro-9-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ;
- 30 10) 6-Fluoro-9-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid ;
- 11) 2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic acid;
- 12) 2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
- 35 13) Ethyl 2-fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate;
- 14) 2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
- 15) Ethyl 2,4-difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate;
- 40 16) 2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic acid;
- 17) 2-Fluoro-5-[[3-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
- 45 18) 2-Fluoro-5-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid; and pharmaceutically acceptable salts thereof.

The structural formulae of the above numbered compound, indicated according to their progressive number, are reported in the following table.

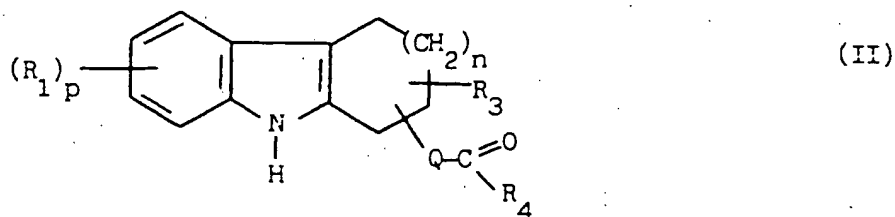
50

55

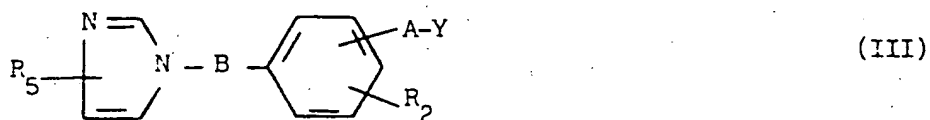
Compound	A	B	Position of B on Phenyl	Q	Position of Q	n	R ₁	R ₂	R ₃	R ₄	R ₅
1	CH ₃	BOND	para	CH ₃	a	1	2F	H	H	OH	H
2	CH ₃	BOND	para	CH ₃	a	1	2F	H	H	OEt	H
3	CH ₃	BOND	para	CH ₃	a	1	2F	H	H	NH ₂	H
4	CH ₃	BOND	para	CH ₃	a	1	2F, 4F	H	H	OH	H
5	CH ₃	BOND	para	CH ₃	a	1	2F, 4F	H	H	OEt	H
6	CH ₃	BOND	meta	CH ₃	a	1	2F	H	H	OH	H
7	CH ₃	BOND	para	CH ₃	b	1	2F	H	H	OH	H
8	CH ₃	BOND	para	CH ₃	b	1	2F, 4F	H	H	OH	H
9	CH ₃	CH ₃	para	CH ₃	a	1	2F	H	H	OH	H

Compound	A	B	Position of B on Phenyl	Q	Position of Q	n	R ₁	R ₂	R ₃	R ₄	R ₅
10	CH ₃	CH ₃	para	CH ₃	b	1	2F	H	H	OH	H
11	CH ₃	BOND	para	CH ₃	a	2	2F	H	H	OH	H
12	CH ₃	BOND	para	CH ₃	b	2	2F	H	H	OH	H
13	CH ₃	BOND	para	CH ₃	b	2	2F	H	H	OEt	H
14	CH ₃	BOND	para	CH ₃	b	2	2F, 4F	H	H	OH	H
15	CH ₃	BOND	para	CH ₃	b	2	2F, 4F	H	H	OEt	H
16	CH ₃	BOND	para	CH ₃	a	2	2F, 4F	H	H	OH	H
17	CH ₃	BOND	meta	CH ₃	b	2	2F	H	H	OH	H
18	CH ₃	CH ₃	para	CH ₃	b	2	2F	H	H	OH	H

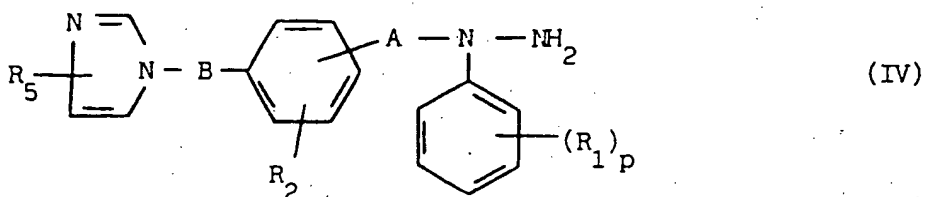
The compound of the invention and the salts thereof can be obtained by a process comprising:
 a) reacting a compound of formula (II) or a salt thereof.



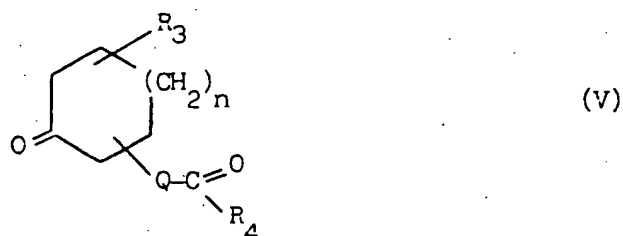
10 wherein n, p, Q, R₁, R₃ and R₄ are as defined above, with a compound of formula (III).



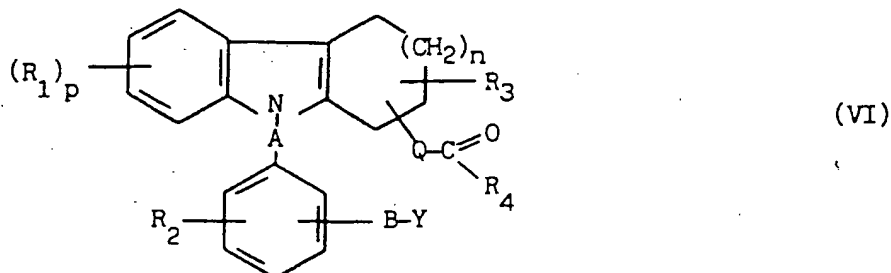
20 wherein A, B, R₂ and R₅ are as defined above and Y is a leaving group; or
b) reacting a compound of formula (IV)



30 wherein p, A, B, R₁, R₂ and R₅ are as defined above, with a compound of formula (V)



40 wherein n, Q, R₃ and R₄ are as defined above; or
c) reacting a compound of formula (VI) or a salt thereof



55 where n, p, A, B, Q, R₁, R₂, R₃, R₄ are as defined above and Y is a leaving group, with imidazole, C₁-C₄ alkylimidazole or a salt thereof, and if desired, converting a compound of formula (I) into another

compound of formula (I), and/or, if desired converting a compound of formula (I) into a salt thereof, and/or, if desired, converting a salt of a compound of formula (I) into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers.

A leaving group Y in a compound of formula (III) or of formula (VI) is preferably a halogen e.g. bromine, chlorine or a mesyl or a tosyl group.

The reaction of a compound of formula (II) with a compound of formula (III) can be carried out using a strong base such as sodium hydroxide, potassium t-butoxide, potassium hydride, ethyl magnesium bromide or potassium hexamethyldisilazide in the presence of a suitable organic solvent such as dimethylformamide, dimethylacetamide, tetrahydrofuran, toluene, ethyl acetate, benzene, or a mixture of two of them, at a temperature ranging from about -20 °C to about 50 °C.

The reaction of a compound of formula (IV) with a compound of formula (V) can be carried out using the standard conditions of the Fisher indolic synthesis (a well known reaction described, for example, in "Heterocyclic Compounds", 25, parts I, II and III, W.J. Houlihan, ed, Interscience, John Wiley & Sons, New York, 1979) e.g. by operating at reflux temperature in an organic solvent, e.g. methanol, ethanol, isopropyl alcohol, benzene or toluene. The reaction may be performed in the presence of an acid catalyst, e.g. sulphuric acid or hydrochloric acid.

The reaction of a compound of formula (VI) with imidazole or C₁-C₄ alkylimidazole can be carried out in the presence of a base such as triethylamine or, preferably, using an excess of imidazole.

When a compound of formula (VI) is reacted with a salt of imidazole or C₁-C₄ alkyl imidazole, the salt is e.g. a potassium or sodium salt and the reaction does not require the presence of any additional basic agent.

The reaction is performed in the presence of a suitable organic solvent such as ethanol, methanol, dimethylformamide, dimethylacetamide, or in the absence of a solvent, e.g. in fusion with an excess of imidazole or C₁-C₄ alkylimidazole, at a temperature ranging from about 70 °C to about 170 °C. When in a compound of formula (VI) B is a direct linkage the reaction can be performed in radicalic condition using a catalyst such as Cu₂Br₂ or Cu powder.

A compound of formula (I) may be converted, if desired, into another compound of formula (I).

These optional conversions may be carried out by methods known in themselves.

A compound of formula (I) containing an esterified carboxy group, may be converted into a compound of formula (I) containing a free carboxy group, by acidic or alkaline hydrolysis, operating at a temperature ranging from room temperature to about 100 °C.

A compound of formula (I) containing a free carboxy group, may be converted into a compound of formula (I) containing an esterified carboxy group by esterification, e.g. via the corresponding acid halide, e.g. chloride, reacting with an excess of a suitable C₁-C₄ alkyl alcohol or by direct esterification by means of acidic catalysis i.e. in the presence of dry HCl or SOCl₂ or BF₃-etherate.

A compound of formula (I) containing a free or esterified carboxy group may be converted into a compound of formula (I) containing a -CONR₆ -R₇ group, wherein R₆ and R₇ are as defined above. Accordingly, the conversion of an esterified carboxy group into the corresponding amide may be performed by direct reaction with ammonia or an appropriate amine in a suitable aprotic solvent, e.g., ether or benzene or using an excess of the amine as solvent, at a temperature ranging from room temperature to reflux.

The conversion of a free carboxy group into a corresponding amide may be carried out via an intermediate reactive derivatives which may be isolated or not.

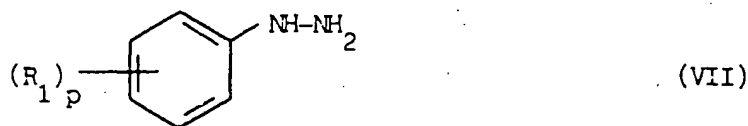
Intermediate reactive derivatives may be active esters e.g. NO₂-phenyl esters, or N-hydroxysuccinimide ester, acid halides, preferably chloride, mixed anhydrides e.g. ethoxycarbonyl or tert-butylcarbonyl anhydrides, or the reactive intermediate obtained in situ by reaction of the acid with dicyclohexylcarbodiimide or carbonyldiimidazole.

The reactive intermediates obtained following conventional routes, such as those usually employed in the synthesis of peptides, are reacted with ammonia or an appropriate amine in a suitable solvent or with an excess of the amine itself at temperatures ranging from about -10 °C to about 50 °C.

The optional salification of a compound of formula (I) as well as the conversion of a salt into a free compound and the separation of a mixture of isomers into the single isomers may be carried out by conventional methods.

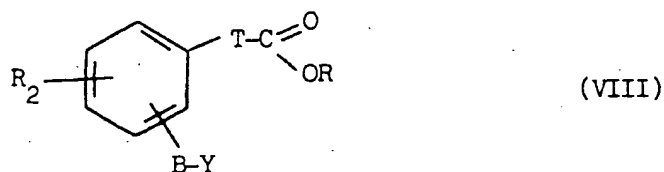
For example the separation of a mixture of geometric isomers, e.g. cis - and trans - isomers, may be carried out by fractional crystallization from a suitable solvent or by chromatography, either column chromatography or high pressure liquid chromatography.

A compound of formula (II) may be obtained by reacting a compound of formula (VII)



wherein R_1 and p are as defined above, with a compound of formula (V) as defined above using the standard conditions of Fisher indolic synthesis as described above.

A compound of formula (III) can be obtained by reacting a compound of formula (VIII)



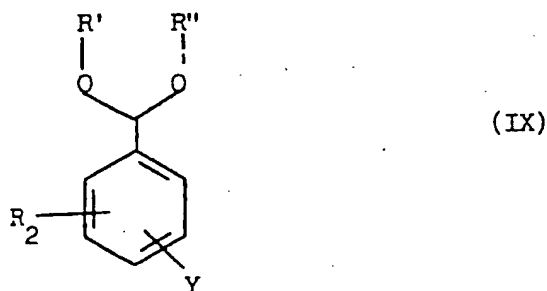
wherein B and Y are as defined above, T is a direct linkage or a straight or branched C_1 - C_3 alkylene chain and R is a lower, e.g. C_1 - C_4 alkyl group, with imidazole, C_1 - C_4 alkylimidazole or a salt thereof.

The reaction can be carried out in the presence of a base such as triethylamine, or preferably using an excess of imidazole or C_1 - C_2 alkylimidazole in a suitable organic solvent such as ethanol, methanol, dimethylformamide, dimethylacetamide, or in the absence of a solvent, e.g. in fusion with excess of imidazole or C_1 - C_2 alkylimidazole, at temperatures ranging from about 70°C to about 165°C .

If required a catalyst, e.g. CuBr or Cu can additionally be used in the above said reaction.

The imidazole ring containing ester so obtained can, by usual and well known methods, be transformed into a compound of formula (III), e.g. reducing with LiAlH_4 and halogenating the so obtained alcohols with SOCl_2 , SOBr_2 or PCl_5 .

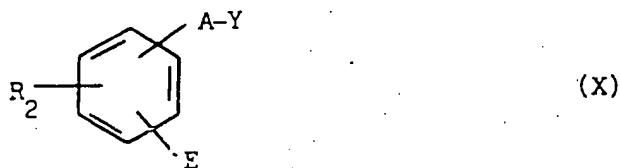
Alternatively a compound of formula (III) wherein B is a direct linkage and A is $-\text{CH}_2-$ can be obtained by reacting a compound of formula (IX)



wherein R_2 and Y are as defined above, and wherein R' and R'' are C_1 - C_6 alkyl groups or taken together with the oxygen atoms to which they are attached form a 1,3-dioxolane or a 1,3 dioxane ring, with imidazole, C_1 - C_4 alkylimidazole or preferably with its sodium or potassium salt, in presence of Cu_2Br_2 or Cu powder, using a suitable organic solvent such as dimethylformamide, dimethylacetamide or dimethoxyethane at temperatures ranging from about 100° to about 200°C . The substituted benzaldehyde ketal so obtained can be transformed into a compound of formula (III) following well known methods e.g. hydrolysis of acetal group in acid condition, reduction of aldehyde with NaBH_4 or LiAlH_4 and halogenation with SOCl_2 or SOBr_2 .

The compounds of formula (IV) are obtainable following the known methods of N -alkylation of phenylhydrazine using compounds of formula (III) as alkylating agents.

A compound of formula VI may be obtained by reacting a compound of formula (II) with a compound of formula (X)



wherein E is either Y, as defined above, or a chemical precursor of a group B-Y, wherein B and Y are as defined above, thus obtaining, respectively, a compound of formula (VI) wherein B is a direct linkage or, after converting the chemical precursor in a B-Y group by the well known methods in the art, a compound of formula (VI) wherein B is a C₁-C₄ alkylene chain.

A chemical precursor of a group B-Y may be for instance a ketal or ester group well known in the art.

The compounds of formula (VII), (VIII), (IX) and (X) are known compounds or may be obtained by procedures well known in organic chemistry.

When in the intermediate compounds, according to the present invention, groups are present which may interfere with the reactions herein described, these groups can be protected before the reaction takes place and then deprotected at the end of the reaction according to known methods, e.g. those used in the chemistry of peptides.

PHARMACOLOGY

Thromboxane (TXA₂) is a derivative of arachidonic acid metabolism that aggregates platelets and amplifies their response to a variety of other aggregating agents.

In addition TXA₂ contracts vascular, bronchial and tracheal smooth muscle cells and glomerular mesangial cells.

Therefore TXA₂ is involved in a variety of pathologies such as: cardiovascular diseases (myocardial infarction and angina), cerebrovascular diseases, (stroke, transient ischemic attack and migraine), peripheral vascular diseases, (microangiopathies), renal diseases (glomerulosclerosis, lupus nephritis, diabetic nephropathy), and respiratory diseases (bronchoconstriction and asthma) and more in general is involved in atherosclerosis.

TXA₂ exerts its action in platelet and smooth muscle cells through the occupancy of receptor(s), the TXA₂ receptor(s).

The effects of TXA₂ can be counteracted by an agent possessing TXA₂ receptor antagonistic properties and/or by an agent inhibiting the enzymes involved in the synthesis of TXA₂, in particular TXA₂-synthase which catalyses the formation of TXA₂ from cyclic endoperoxides prostaglandin G₂ and prostaglandin H₂ without affecting the synthesis of other prostaglandins.

Agents which inhibit TXA₂ action either by antagonizing TXA₂ and/or inhibiting TXA₂-synthase may be expected to be of therapeutic value in the treatment of the above-mentioned diseases and in other pathological conditions in which TXA₂ is involved.

Therefore the compounds of the present invention, which possess these activities, are believed to be effective in the treatment of a disease state in which an enhancement of TXA₂ synthesis exerts a pathogenic effect, for instance those mentioned above.

METHODS.

The effects of a representative group of compounds of the invention were evaluated, in comparison with known compounds, on TxB₂ synthesis inhibition in vitro, in whole blood of normal rats, and on TxA₂ antagonism in a binding assay in washed human platelets.

TxB₂ synthesis inhibition

Blood was withdrawn from the abdominal aorta of normal Sprague Dawley rats (Charles River Italy) under light ether anaesthesia. The blood was immediately divided in portions of 0.5 ml and distributed in glass tubes each containing a concentration of the test compound, or of the reference compounds.

Samples were then allowed to clot for 1 hour at 37°C, centrifuged at 3000 rpm for 10 min, and serum collected and stored at -20°C until assayed. TxB₂ levels were determined by RIA according to previously described procedures (Thromb. Res. 17, 3/4, 317, 1980) using highly sensitive antibody.

Displacement of [³H]-SQ 29,548 binding to washed human platelets

Blood from healthy volunteers of both sexes who had not taken any medication for at least 10 days was collected into one-tenth volume of acid citrate dextrose containing indomethacin (28 μ M). Platelet rich plasma (PRP), obtained by centrifugation of the blood at 200xg for 20 min, was washed twice (1000xg for 10 min). The platelets are then resuspended in Tyrode-Hepes buffer, (pH 7.4) to a final concentration of $5 \cdot 10 \times 10^{-8}$ cells/ml and incubated for 0-60 min at 25° with [³H]-SQ 29,548 (5 nM). For displacement experiments various concentrations (10^{-9} - 10^{-4} M) of competing ligands were added and incubated for 30 min at 25° C.

Non-specific binding was determined in the presence of 50 μ M U46619 and was approximately 5% of total binding of [³H]-SQ 29,548. After the incubation, 4 ml of ice-cold TRIS-HCl buffer (10 mM, pH 7.4) was added to each tube and the reaction mixture was immediately filtered by suction through a Whatman GF/C glass filter disc which was washed 2 times with ice-cold TRIS-HCl (4 ml) and counted for radioactivity by a Packard β -counter.

The binding data were analysed by computerized non-linear curve fitting using the Ligand program and expressed as IC₅₀.

In Table 1, as an example the results obtained with the compounds, according to the present invention, having internal codes FCE 26643 and FCE 27041, in the binding test (washed human platelets) are compared to those obtained with the reference standard compounds, BM 13505 and BM 13177 (Naunyn-Schmiedeberg's Arch. Pharmacol. 1986, 332 (Suppl.) Abst. 144 S.R. 36; Cardiovasc. Drug Rev. 1988, 6:20-34).

These results show that the compounds FCE 26643 and FCE 27041 have an affinity for the receptor greater than those of compounds BM 13505 and BM 13177.

Table 1

³ H SQ 29548 binding displacement (washed human platelet) IC ₅₀ (M)	
BM 13505	1.2×10^{-7}
BM 13177	7.3×10^{-6}
FCE 26643	6.6×10^{-9}
FCE 27041	6.00×10^{-9}

In table 2, as an example, the results obtained with the compound of the invention having internal code FCE 27041, on Tx_{B2} synthesis in normal rats, are compared with those obtained with the reference standard dazoxiben and ASA; limits when calculated are reported in brackets.

Table 2

In vitro effect on Tx _{B2} synthesis in normal rats. Data are expressed as IC ₅₀ (M) and limits for p = 0.95		
Compound	IC ₅₀ (M) (whole blood)	LIMITS
FCE 27041	1.98×10^{-7}	$(1.21-3.57 \times 10^{-7})$
Dazoxiben	1.2×10^{-6}	$(0.7-1.9 \times 10^{-6})$
ASA	3.1×10^{-5}	$(2.6-3.8 \times 10^{-5})$

In the above table 1 and 2 internal code FCE 26643 means 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]-methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid; FCE 27041 means 2-Fluoro-5-[[4-(1H-imidazol-1-yl)-phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid; and ASA means acetylsalicylic acid.

As the compounds of the present invention are both Tx_{A2} synthase inhibitors and PGH₂/Tx_{A2} antagonists in the platelets, on the basis of the state of the art, as reported e.g. in J. Clin. Invest. 80, 1435 (1987) and in Adv. Prostaglandins, Thromboxanes, Leukotrienes Res. Vol. 17 (1987) p. 49, these compounds are particularly suitable for the treatment of a disease state in which an enhancement of Tx_{A2} synthesis exerts a pathogenic effect, for instance in those mentioned above.

In particular in the treatment of renal failure the compounds of the invention may be used in association with an angiotensin converting enzyme inhibitor (ACEI), both as separated and substantially concomitant administration. The compounds of the invention can also be used to prevent or treat cyclosporin A-induced

nephrosis in mammals.

The compounds of the invention can also be used in association with thrombolytic agents (e.g. tPA, Streptokinase, pro-Urokinase) in order to reduce the dose of the latter required in thrombolytic therapy, and to lower the incidence of reocclusion and possibly haemorrhage.

5 A further application of the compounds of the invention is the prevention and/or treatment of restenosis after percutaneous transluminal angioplasty.

The toxicity of the compounds of the invention is negligible, therefore they can be safely used in therapy.

10 Mice and rats which had been deprived of food for nine hours were treated orally with single administrations of increasing doses of compounds of the invention, then housed and normally fed. In view of their high activity the compounds of the invention can be safely used in medicine.

The therapeutic regimen for the different clinical syndromes must be adapted to the type of pathology, taking into account, as usual, also the route of administration, the form in which the compound is administered and the age, weight and conditions of the subject involved. The oral route is employed, in
15 general, for all conditions requiring such compounds. Preference is given to intravenous injection or infusion for the treatment of acute pathological states. For maintenance regimens the oral or parental, e.g. intramuscular, route is preferred.

The dosage level suitable for oral administration to adult humans of the compounds of the invention, e.g. 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, may range
20 from about 50 mg to about 500 mg per dose 1 to 3 times a day.

Of course, these dosage regimens may be adjusted to provide the optimal therapeutic response.

The nature of the pharmaceutical compositions containing the compounds of this invention in association with pharmaceutically acceptable carriers or diluents will of course, dependent upon the desired route of administration.

25 The compositions may be formulated in the conventional manner with the usual ingredients. For example, the compounds of the invention may be administered in the form of aqueous or oily solutions, or suspensions, tablets, pills, gelatine capsules, syrups, drops or suppositories.

Thus, for oral administration, the pharmaceutical composition containing the compounds of this invention are preferably tablets, pills or gelatine capsules which contain the active substance together with
30 diluents, such as lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, for instance silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; or they may also contain binders, such as starches, gelatine, methylcellulose, carboxymethylcellulose, gum-arabic, tragacanth, polyvinylpyrrolidone; disaggregating agents, such as starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and in
35 general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Said pharmaceutical preparations may be manufactured in known manner, for example by means of mixing, granulating, tableting, sugar-coating, or film-coating processes. The liquid dispersions for oral administration may be e.g. syrups, emulsions and suspensions.

40 The syrups may contain as carrier, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

The suspensions and the emulsions may contain as carrier, for example, a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain together with the active compound a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable
45 amount of lidocaine hydrochloride.

The solutions for intravenous injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile aqueous isotonic saline solutions.

The suppositories may contain together with the active compound a pharmaceutically acceptable carrier e.g. cocoa-butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

50 The following examples illustrate but do not limit the present invention.

EXAMPLE I

6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

55 A solution of 740 mg of 6-fluoro-1,2,3,4-tetrahydro carbazol-1-yl-acetic acid in 20 ml of dry DMF is treated with 270 mg of 80% NaH. The reaction mixture is stirred for 10 minutes at room temperature, then 685 mg of 1-[4-(chloromethyl)phenyl]-1H-imidazole hydrochloride are added portionwise.

The mixture is stirred at room temperature for 3 hours, then evaporated to dryness at reduced pressure.

The residue is taken up with water, washed with AcOEt, neutralized with AcOH, and the resulting precipitated is filtered and dried to give 700 mg of the title compound.

m.p. 142-143 °C.

N.M.R (DMSO-d₆) p.p.m.: 1.80-2.10(4H,m,CH₂-CH₂-CH), 2.35-2.9(4H,m,CH₂-COOH + CH₂-C=C-N) 3.40-
 5 (1H,m,CH-CH₂-COOH), 5.27 (1H,d,CHHN) 5.40(1H,d,CHHN), 6.80-7.30(9H, m, benzene H and N-CH=CH-N), 8.21 (1H,s,N=CH-N)

Analogously the following compounds can be prepared:

6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, m.p. 113-115 °C.

10 N.M.R. (CDCl₃-d₆) p.p.m.: 1.70-2.10 (4H,m,CH₂-CH₂-CH), 2.40-2.85 (4H,m,CH₂-COOH + CH₂-C=C-N) 3.40- (1H,m,CH-CH₂-COOH), 5.40 (1H,d,CHHN) 5.54 (1H,d,CHHN), 6.50-7.30 (8H,m,benzene H and N-CH=CH-N), 7.90 (1H,s,N=CH-N);

6-Fluoro-9-[[3-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, m.p. 225 °C;

6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid;

15 6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-2-yl acetic acid;

6-Fluoro-9-[[4-(1H-imidazol-1-yl-methyl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;

6-Fluoro-9-[[4-(1H-imidazol-1-yl-methyl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid;

6-Bromo-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, m.p. 238-240 °C;

6-Chloro-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, and

20 6,8-Dichloro-9-[[4-(1H-imidazol-1-yl)phenyl)methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

The 6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid used above is prepared as follows:

A mixture of isopropyl 6-fluoro-1,2,3,4-tetrahydrocarbazole-1-yl-acetate (1.4 g), 1N sodiumhydroxide (20 ml) and methanol (20 ml) is refluxed for 4 hours.

25 After cooling the reaction mixture is poured into water, washed with methylene chloride, acidified with 1N HCl and extracted with methylene chloride. The organic layer, dried and evaporated, affords 1.1 g of 6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

The isopropyl 6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetate used above is prepared as follows:

A mixture of 1-(4-fluorophenyl)hydrazine hydrochloride (5 g), ethyl 2-cyclohexanoneacetate (5.6 g) and 2-propanol (100 ml) is refluxed under nitrogen for 9 hours. After cooling the mixture is filtered and the solution
 30 evaporated to dryness. The residue is purified through a silica gel column eluting with methylene chloride/methanol (100/1) to give 4 g of isopropyl 6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl- acetate.

The 1-[4-(chloromethyl)phenyl]-1H-imidazole hydrochloride used above is prepared as follow:

To a solution of 4-(1-imidazolyl)benzaldehyde (2.5 g) in methanol (20 ml), 1.5 g of NaBH₄ is added.

35 After stirring at room temperature for 3 hours the mixture is poured into water and extracted with methylene chloride.

The organic phase is dried and evaporated to dryness to yield 2.0 g of 4-(1-imidazolyl)-benzylalcohol. Alternatively the 4-(1-imidazolyl)-benzylalcohol can be obtained by reduction of the ethyl 4-(1-imidazolyl)-benzoate with LiAlH₄.

40 The 4-(1-imidazolyl)-benzylalcohol thus obtained is solved in diethyl ether and transformed into the corresponding hydrochloride by bubbling gaseous HCl.

Filtration yields 2.4 g of the salt which is suspended in 30 ml of benzene and treated with 0.8 ml of SOCl₂ and refluxed for 3 hours. The mixture is evaporated to dryness, taken up with ethyl ether and filtered to give 2.6 g of 1-[4-(chloromethyl)phenyl]-1H-imidazole hydrochloride, m.p. 176-178 °C.

The 4-(1-imidazolyl)benzaldehyde used above is prepared as follows:

45 7.36 g of p-bromobenzaldehyde is treated at reflux with ethylene glycol in benzene to obtain the corresponding acetate. 8.51 g of this acetate are added to a solution of 5.12 g of imidazole sodium salt in 100 ml of DMF then 3.63 g of Cu powder are added and the mixture is refluxed for 6 hours, cooled, poured into diluted chloridic acid and crushed ice. The mixture is warmed at 50 °C for 1 hour, cooled, washed with methylene chloride, neutralized with NaHCO₃, extracted with methylene chloride, dried and evaporated to
 50 dryness to give 2.5 g 4-(1-imidazolyl) benzaldehyde.

The ethyl-4-(1-imidazolyl)-benzoate is obtained in good yield reacting the ethyl 4-bromobenzoate with imidazole in radicalic condition using CuBr as catalyst.

EXAMPLE 2

55

2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl)methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid.

A solution of 122 mg of 2-fluoro- 5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid in 20 ml of dry DMF is cooled at 0 °C, and treated with 102 mg of 55% NaH. The reaction mixture is stirred for 60 minutes

at 0 °C, then 160 mg of 1-[4-(chloro-methyl)phenyl]-1H-imidazole hydrochloride are added portionwise at 0 °C. After stirring at room temperature for 16 hours the mixture is poured into water and washed with methylene chloride. The aqueous solution is neutralized with diluted HCl and extracted with methylene chloride. The organic layer is dried over sodium sulfate and evaporated to dryness. The residue, washed with acetone and dried, yields 116 mg of the title compound m.p. 237 °C.

N.M.R. (DMSO-d₆) δ p.p.m.: 1.4-2.1(5H, m, CH₂-CH₂-CH), 2.2(2H, m, CH₂-COOH), 2.5-3.05(4H, m, CH₂-C=C-CH₂), 5.42(2H, bs, NCH₂), 6.8-7.65(9H, m, benzene H and N-CH=CH-N), 8.16(1H, s, N=CH-N)

Analogously, the following compounds can be prepared:

2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
 2-Fluoro-5-[[3-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
 2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic acid;
 2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic acid;
 and 2-Fluoro-5-[[4-(1H-imidazol-1-yl)methyl]phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid and pharmaceutically acceptable salt thereof.

The 2-fluoro-5,6,7,8,9,10-hexahydro-cyclohept[b]indole-7-acetic acid used above is prepared analogously as reported in example 1 for the preparation of the 6-fluoro-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

EXAMPLE 3

Ethyl 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate.

To a solution of hydrogen chloride in absolute ethanol (50 ml), 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (0.5 g) is added. The reaction mixture is heated at 60 °C for 5 hours and then evaporated under reduced pressure to dryness.

The residue is taken up with water, the solution is treated with NaHCO₃, then added of CH₃COOH, extracted with CH₂Cl₂ and evaporated to dryness to give 0.4 of the title compound,
 N.M.R. (CDCl₃-d₆) p.p.m.: 1.22 (3H, t, COOCH₂CH₃) 1.70-2.00 (4H, m, CH₂-CH₂-CH) 2.30-2.9 (4H, m, CH₂-COOH + CH₂-C=C-N) 3.40 (1H, m, CH-CH₂-COOH), 4.1 (2H, m, CH₂CH₃) 5.27 (1H, d, CHHN), 5.35 (1H, d, CHHN) 6.80-7.30 (9H, m, benzene H and N-CH=CH-N) 7.79 (1H, s, N=CH-N).

Analogously, the following compounds can be prepared:

Ethyl 6,8-difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate;
 Ethyl 2-fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate;
 and
 Ethyl 2,4-difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate.

EXAMPLE 4

6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetamide

A suspension of 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid (1.0g) in DMF (10ml) is treated with SOCl₂ (0.5 g) and, after cooling a gaseous NH₃ is passed through the reaction mixture for 6 hours. The ammonium salt is filtered off and ether is added to the solution. The so obtained precipitated is filtered and dried to give 0.8g of the title compound.

EXAMPLE 5

6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid.

A mixture of 1-[(4-1H-imidazol-1-yl)benzyl]-1-(4-fluorophenyl)hydrazine hydrochloride (1.7 g), ethyl 2-cyclohexanoneacetate (1 g) and 2-propanol (100 ml) is refluxed under nitrogen for 9 hours. After cooling the reaction mixture is evaporated to dryness. The resulting residue is purified through a silica gel column eluting with methylene chloride/methanol (95/5) to give 0.6 g of a mixture of Ethyl 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate and isopropyl 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate.

The mixture of ethyl and isopropyl esters is added of methanol (30 ml), water (30 ml) and potassium hydroxide (0.5 g). The resulting mixture is refluxed for 6 hours.

After cooling the methanol is evaporated under reduced pressure and the resulting aqueous solution is neutralized with HCl solution and acidified with acetic acid.

The resulting solid is filtered, washed with water and dried to yield 0.4 g of the title compound, m.p. 142-143 °C.

Analogously the following compounds can be prepared:

6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, m.p. 113-115°C, and

6-Fluoro-9-[[3-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, m.p. 225°C.

5 The 1-[[4-(1H-imidazol-1-yl)benzyl]-1-(4-fluorophenyl)hydrazine hydrochloride used above is prepared as follows:

a mixture of 1-(4-fluorophenyl)hydrazine hydrochloride (3.3 g), 1-[4-(chloromethyl)phenyl]-1H-imidazole hydrochloride (3.1 g), triethylamine (6.6 ml) and toluene (200 ml) is refluxed under nitrogen for 13 hours. After cooling the mixture is filtered and the solution is evaporated to dryness. The residue is purified
10 through a silica gel column eluting with methylene chloride/methanol (100/5) to give 2.0 g of 1-[[4-(1H-imidazol-1-yl)benzyl]-1-(4-fluorophenyl)hydrazine hydrochloride, ms: m/e 282 (M⁺), 158, 157.

EXAMPLE 6

15 Tablets, each weighing 150 mg and containing 50 mg of the active substance can be manufactured as follows:

Composition (for 10,000 tablets)

6-fluoro-9[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid 500 g

20

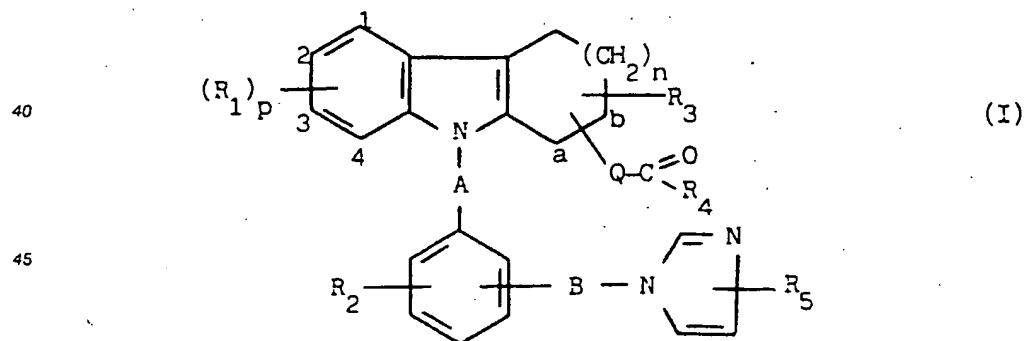
Lactose	710 g
Corn starch	237.5 g
Talc powder	37.5 g
Magnesium stearate	15

25

6-fluoro-9[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, lactose and a half of the corn starch are mixed; the mixture is then forced through a sieve of 0.5 mm openings. Corn starch (18 mg) is suspended in warm water (180 ml). The resulting paste is used to granulate the powder. The granules are dried, comminuted on a sieve of sieve size 1.4 mm, then the remaining quantity of starch,
30 talc and magnesium are added, carefully mixed, and processed into tablets using punches of 8 mm diameter.

Claims

35 1. A compound of formula (I)



50

wherein

n is 1 or 2;

p is an integer of 1 to 4;

A is a straight or branched C₁-C₄ alkylene chain;

B is a direct linkage, a straight or branched, unsaturated or saturated C₁-C₄ alkylene chain;

55

Q is a direct linkage or a straight or branched C₁-C₄ alkylene chain;

each of R₁ and R₂ independently is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfonyl, halogen or trihalomethyl;

each of R₃ and R₅, independently is hydrogen or C₁-C₄ alkyl;

R₄ is -OR₆ or -N(R₆,R₇) group, wherein each of R₆ and R₇ independently is hydrogen, C₁-C₄ alkyl, phenyl or benzyl; or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I), according to claim 1, wherein each of n and p independently is 1 or 2;
 - 5 A is -CH₂- or -CH₂-CH₂-;
 - B is direct linkage or -CH₂-;
 - Q is direct linkage, -CH₂- or -CH₂-CH₂-; each of R₁, R₂, independently is hydrogen, C₁-C₄ alkyl, halogen or trifluoromethyl;
 - R₃ and R₅ are hydrogen;
 - 10 R₄ is -OR₆ or -NHR₆ wherein R₆ is hydrogen or C₁-C₄ alkyl or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I), according to claim 1, wherein each of n and p independently is 1 or 2;
 - 15 A is -CH₂-;
 - B direct linkage or -CH₂-;
 - Q is -CH₂-;
 - R₂, R₃ and R₅ are hydrogen;
 - R₁ is halogen or trifluoromethyl;
 - R₄ is OR₆ or NHR₆ wherein R₆ is hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof.
 - 20

4. A compound selected from the group consisting of:
 - 25 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ;
 - Ethyl 6-fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl] 2)-1,2,3,4-tetrahydrocarbazol-1-yl-acetate;
 - 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetamide;
 - 30 6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
 - Ethyl 6,8-difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetate;
 - 6-Fluoro-9-[[3-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid ;
 - 35 6-Fluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid ;
 - 6,8-Difluoro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid;
 - 40 6-Fluoro-9-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
 - 6-Fluoro-9-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-2-yl-acetic acid ;
 - 45 2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic acid;
 - 2-Fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
 - Ethyl 2-fluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate;
 - 50 2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;
 - 6-Bromo-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid;
 - 55 Ethyl 2,4-difluoro-5-[[4-(1H-imidazol-1-yl) phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetate;
 - 2,4-Difluoro-5-[[4-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-6-acetic

acid;

2-Fluoro-5-[[3-(1H-imidazol-1-yl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;

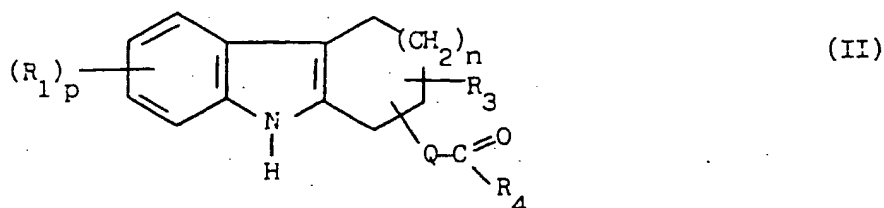
5 2-Fluoro-5-[[4-(1H-imidazol-1-ylmethyl)phenyl]methyl]-5,6,7,8,9,10-hexahydrocyclohept[b]indole-7-acetic acid;

6-Chloro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, and
6,8-Dichloro-9-[[4-(1H-imidazol-1-yl)phenyl]methyl]-1,2,3,4-tetrahydrocarbazol-1-yl-acetic acid, and the
10 pharmaceutically acceptable salts thereof.

5. A process for the preparation of a compound of formula (I) or a salt thereof, according to claim 1, the process comprising:

a) reacting a compound of formula (II) or a salt thereof

15

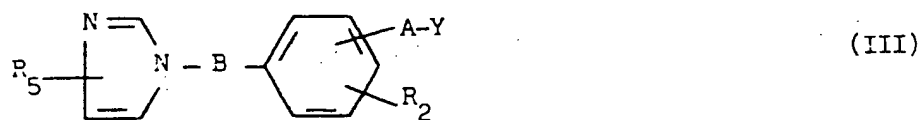


20

25

wherein n, p, Q, R₁, R₃ and R₄ are as defined in claim 1, with a compound of formula (III).

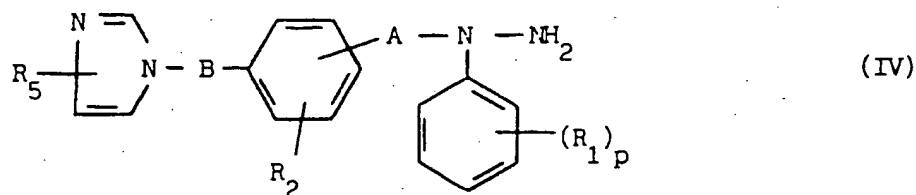
30



wherein A, B, R₂ and R₅ are as defined in claim 1, and Y is a leaving group; or
b) reacting a compound of formula (IV)

35

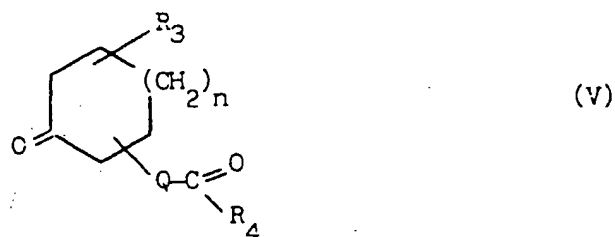
40



45

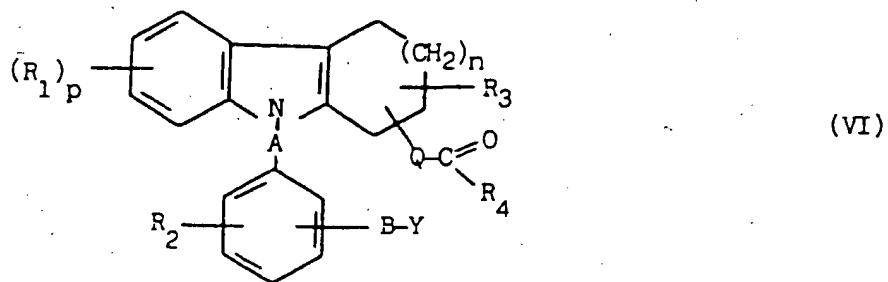
wherein p, A, B, R₁, R₂ and R₅ are as defined in claim 1, with a compound of formula (V).

50



55

wherein n, Q, R₃ and R₄ are as defined in claim 1; or
c) reacting a compound of formula (VI) or a salt thereof



wherein n , p , A , B , Q , R_1 , R_2 , R_3 , R_4 are as defined in claim 1, and Y is a leaving group, with imidazole, C_1 - C_4 alkylimidazole or a salt thereof, and if desired, converting a compound of formula (I) into another compound of formula (I), and/or, if desired converting a compound of formula (I) into a salt thereof, and/or if desired converting a salt of a compound of formula (I) into a free compound, and/or, if desired, separating a mixture of isomers of a compound of formula (I) into the single isomers.

6. A pharmaceutical composition containing a suitable carrier and/or diluent and, as active principle, a compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof.
7. A compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease state in which an enhancement of TXA_2 synthesis exerts a pathogenic effect.
8. A compound of formula (I), according to claim 1, or a pharmaceutically acceptable salt thereof, for use in the treatment of cardiovascular disease, cerebrovascular disease, peripheral vascular disease, renal disease, respiratory disease or atherosclerosis.

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) Publication number:

0 496 237 A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 92100414.9

(51) Int. Cl.⁵: C07D 403/10, A61K 31/415

(22) Date of filing: 13.01.92

(30) Priority: 22.01.91 GB 9101375

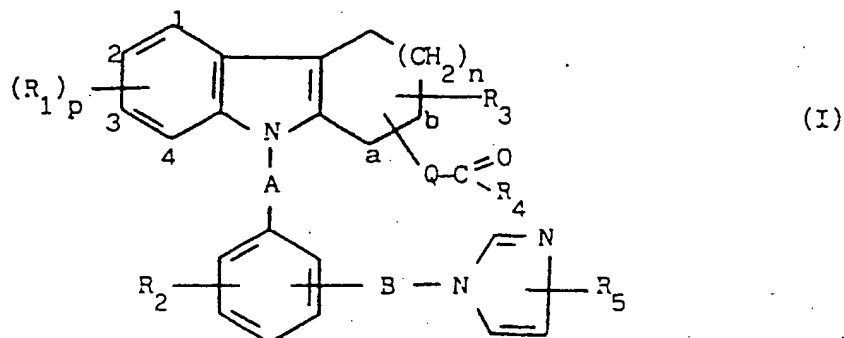
(43) Date of publication of application:
29.07.92 Bulletin 92/31(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI NL PT SE(88) Date of deferred publication of the search report:
09.12.92 Bulletin 92/50(71) Applicant: FARMITALIA CARLO ERBA S.r.L.
Via Carlo Imbonati 24
I-20159 Milano(IT)(72) Inventor: Cozzi, Paolo
via Zanella 48/5
I-20133 Milan(IT)

Inventor: Pillan, Antonio
via Milani 1
I-20133 Milan(IT)
Inventor: Pulici, Maurizio
via Giovanni Pascoli 1
I-20056 Grezzago (Milan)(IT)
Inventor: Salvati, Patricia
via Valera 16
I-20020 Arese (Milan)(IT)
Inventor: Volpi, Angelo Daniele
via Cascina Croce 204
I-20010 Cornaredo (Milan)(IT)

(74) Representative: Ferrario, Vittorino (IT)
c/o Farmitalia Carlo Erba S.p.A. Via Carlo
Imbonati 24
I-20159 Milano(IT)

(54) N-imidazolyl derivatives of substituted tetrahydrocarbazole and cyclohept[b]indole.

(57) The invention provides new N-imidazolyl derivatives of substituted tetrahydrocarbazoles and cyclopent[b]-indoles of general formula (I)



wherein

n is 1 or 2;

p is an integer of 1 to 4;

A is a straight or branched C₁-C₄ alkylene chain;B is a direct linkage, a straight or branched, unsaturated or saturated C₁-C₄ alkylene chain;Q is a direct linkage or a straight or branched C₁-C₄ alkylene chain;

EP 0 496 237 A3

each of R_1 and R_2 independently is hydrogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfonyl, halogen or trihalomethyl;

each of R_3 and R_5 , independently is hydrogen or C_1 - C_4 alkyl; R_4 is $-OR_6$ or $-N(R_6, R_7)$ group, wherein each of R_6 and R_7 independently is hydrogen, C_1 - C_4 alkyl, phenyl or benzyl; or a pharmaceutically acceptable salt thereof, which are useful in the treatment of a disease state in which an enhancement of TxA_2 synthesis exerts a pathogenic effect.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 0414

Page 1

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 363 789 (FARMITALIA) 18 April 1990 * the whole document * ---	1-8	C07D403/10 A61K31/415
A	ANNU. REP. MED. CHEM vol. 22, 1987, pages 95 - 105 * the whole document * ---	1-8	
A	ANNU. REP. MED. CHEM. vol. 25, 1990, pages 99 - 108 * the whole document * ---	1-8	
A	EP-A-0 073 663 (PFIZER) 9 March 1983 * the whole document * ---	1-8	
A	EP-A-0 234 708 (MERCK FROST CANADA) 2 September 1987 * the whole document * ---	1-8	
A	EP-A-0 310 179 (MERCK FROST CANADA) 5 April 1989 * the whole document * ---	1-8	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07D
A	EP-A-0 107 618 (CIBA-GEIGY) 2 May 1984 * claim 1 * * page 7, paragraph 2 * ---	1-8	
A	FR-A-976 484 (CIBA-GEIGY) 19 March 1951 * example 2 * ---	1-8	
		-/--	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 OCTOBER 1992	Examiner Bernd Kissler
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document			



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 10 0414
Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	US-A-3 970 757 (P. E. CROSS, P. DICKINSON, J. E. G. KEMP) 20 July 1976 * formula (I) * * column 4, line 57 - line 59 * -----	1-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14 OCTOBER 1992	Examiner Bernd Kissler
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons * : member of the same patent family, corresponding document			